

What is claimed is:

1. A process for preparing amorphous form of valsartan comprising the steps of:
  - a) precipitating amorphous valsartan from a solution of valsartan in a solvent selected from the group consisting of methyl t-butyl ether and acetone; and
  - b) recovering valsartan amorphous form.
- 5 2. The process of claim 1, wherein the solvent is methyl t-butyl ether.
3. A process for preparing amorphous form of valsartan comprising the steps of:
  - a) precipitating amorphous valsartan from a mixture of water and a solvent selected from the group consisting of ethanol, DMF, acetone and mixtures thereof; and
  - 10 b) recovering the precipitated amorphous valsartan
4. The process of claim 3, wherein precipitating is carried out by combining water as an anti-solvent with the solution of valsartan in the solvent.
5. A process for preparing amorphous form of valsartan comprising the steps of:
  - 15 a) preparing a solution of valsartan in a solvent selected from the group consisting of tetrahydrofuran, dioxane, ethanol, isopropanol, diethyl ether and methanol; and
  - b) removing the solvent.
6. The process of claim 5, wherein removing is carried out by evaporation.
- 20 7. The process of claim 5, wherein the solvent is selected from the group consisting of tetrahydrofuran, dioxane, ethanol, isopropanol and diethyl ether.
8. A process for preparing amorphous form of valsartan comprising the steps of:
  - a) suspending valsartan in a solvent selected from the group consisting of water and C<sub>5</sub> to C<sub>12</sub> saturated hydrocarbon to obtain amorphous valsartan; and
  - 25 b) recovering the amorphous valsartan.
9. The process of claim 8, wherein the suspending step includes heating.
10. The process of claim 8, wherein the solvent is water.
11. The process of claim 8, wherein the hydrocarbon is heptane or cyclohexane.
- 30 12. A process for preparing amorphous form of valsartan comprising the steps of:
  - a) acidifying a basic aqueous solution of valsartan, wherein the acidifying results in precipitation of amorphous valsartan; and
  - b) recovering the precipitated amorphous valsartan.

13. The process of claim 12, wherein the acidifying results in a pH of from about 2 to about 5.
14. A process for preparing amorphous form of valsartan comprising the steps of:
- 5      a) heating valsartan in diisopropyl ether to obtain amorphous valsartan; and
  - b) recovering the amorphous valsartan.
15. A process for preparing amorphous valsartan comprising the step of heating a crystalline form of valsartan selected from the group consisting of Form III or Form VII.
16. The process of claim 15, wherein the valsartan Form III is prepared by crystallization out of n-butyl acetate.
- 10     17. Amorphous form of valsartan, wherein the amorphous form has a DSC thermogram that lacks a melting point above about 1 J/g.
18. The amorphous valsartan of claim 17, wherein the melting point is lacking in the region of from about 80°C to about 100°C.
19. A process for preparing the crystalline valsartan (Form I) having an XRPD pattern with peaks at 5.4, 13.0, 16.3, 19.5, 20.7, 23.4 ±0.2 degrees 2-theta comprising the steps of:
- 15      a) heating a solution of valsartan in a solvent selected from the group consisting of methyl ethyl ketone and ethyl acetate;
  - b) cooling the solution to a temperature of about negative 20°C to about 20      20°C to induce crystallization; and
  - c) recovering the crystalline valsartan without heating.
20. The process of claim 19, wherein the solvent is methyl ethyl ketone.
21. A process for preparing crystalline valsartan having an XRPD pattern with peaks at about 5.7, 13.6, 18.0 ±0.2 degrees 2-theta (Form VIII) further comprising the step of heating the valsartan of claim 20.
22. A crystalline valsartan (Form II) characterized by an XRPD pattern with peaks at 5.8, 12.7, 14.0, 17.6, 20.8, 22.5 ±0.2 degrees 2-theta
23. The crystalline valsartan of claim 22 having an XRPD pattern as substantially depicted in Figure 5.
- 30     24. A process for preparing crystalline valsartan of claim 22 comprising the steps of:
- a) crystallizing the crystalline valsartan from an emulsion or solution of valsartan in a C<sub>5</sub> to C<sub>12</sub> aromatic hydrocarbon; and
  - b) recovering the crystalline valsartan.

25. The process of claim 24, wherein the aromatic hydrocarbon is toluene.
26. The process of claim 24, further comprising drying the crystalline valsartan.
27. The crystalline valsartan prepared by the process of claim 24.
28. A crystalline valsartan (Form III) with an XRPD pattern with peaks at 5.1, 10.1, 15.3,  
5       $18.6 \pm 0.2$  degrees 2-theta
29. The crystalline valsartan of claim 28 having an XRPD pattern as substantially  
10      depicted in Figure 6.
30. A process for preparing crystalline valsartan of claim 28 comprising the steps of:
  - a)      crystallizing the crystalline valsartan from a solution of valsartan in t-butyl acetate; and
  - b)      recovering the crystalline valsartan.
31. The crystalline valsartan prepared by the process of claim 30.
32. A crystalline valsartan (Form IV) having an XRPD pattern with peaks at 6.2, 10.7,  
14.5, 15.7, 19.0, 23.5,  $24.8 \pm 0.2$  degrees 2-theta.
- 15      33. The crystalline valsartan of claim 32 having an XRPD pattern as substantially  
depicted in Figure 7.
34. A process for preparing crystalline valsartan of claim 32 comprising the steps of:
  - a)      crystallizing the crystalline valsartan from a solution of valsartan in acetonitrile; and
  - 20      b)      recovering the crystalline valsartan.
35. The crystalline valsartan prepared by the process of claim 34.
36. A process for preparing valsartan Form IX further comprising the step of heating the recovered crystalline valsartan of claim 34.
37. A crystalline valsartan (Form VI) characterized by an XRPD pattern with peaks at  
25      5.5, 13.3, 14.3, 17.7, 21.1,  $22.3 \pm 0.2$  degrees 2-theta
38. The crystalline valsartan of claim 37 having an XRPD pattern as substantially  
depicted in Figure 8.
39. A process for preparing the crystalline valsartan of claim 37 comprising the step of  
heating crystalline valsartan Form VII.
- 30      40. The process of claim 39, wherein the Form VII is obtained by crystallization from 2-hexanone.
41. A crystalline valsartan (Form VII) characterized by an XRPD pattern with peaks at  
5.2, 15.2, 15.9, 18.6, 22.8,  $23.6 \pm 0.2$  degrees 2-theta.

42. The crystalline valsartan of claim 41 having an XRPD pattern as substantially depicted in Figure 9.
43. A process for preparing crystalline valsartan of claim 41 comprising the steps of:
- 5       a) Crystallizing the crystalline valsartan from a solution of valsartan in a solvent selected from the group consisting of 2-hexanone and n-butyl acetate; and
- b) recovering the crystalline valsartan.
44. A process for making crystalline valsartan Form VI comprising the step of heating the crystalline valsartan of claim 41.
- 10      45. A crystalline valsartan (Form VIII) characterized by an XRPD pattern with peaks at about 5.7, 13.6, 18.0  $\pm$ 0.2 degrees 2-theta.
46. The crystalline valsartan of claim 45 having an XRPD pattern as substantially depicted in Figure 10.
- 15      47. A process for preparing crystalline valsartan Form VIII comprising the step of heating crystalline valsartan Form I.
48. A crystalline valsartan (Form IX) characterized by an XRPD pattern with peaks at 6.3, 14.0, 17.9  $\pm$ 0.2 degrees 2-theta.
49. The crystalline valsartan of claim 48 having an XRPD pattern as substantially depicted in Figure 11.
- 20      50. A process for preparing crystalline valsartan of claim 48 comprising the step of heating crystalline valsartan Form IV.
51. A process for preparing crystalline valsartan of claim 48 comprising the steps of:
- 25       a) crystallizing the crystalline valsartan from a solution of valsartan in nitromethane; and
- b) recovering the crystalline valsartan.
52. The crystalline valsartan prepared by the process of claim 51.
53. A process for preparing crystalline valsartan of claim 48 comprising the steps of:
- 30       a) crystallizing the crystalline valsartan from a solution of valsartan in acetonitrile;
- b) recovering the crystalline valsartan; and
- c) heating the crystalline valsartan.

54. A crystalline form of valsartan (Form X), wherein the crystalline form is characterized by an XRD pattern with peak at  $5.6 \pm 0.2$  degrees 2 theta and with two broad peaks at 15.0 and 20.6 degrees 2 theta.
55. The crystalline form of claim 54, wherein the crystalline form is characterized by  
5 the XRD pattern as substantially depicted in Figure 20.
56. A process for preparing crystalline valsartan of claim 54 comprising the steps of:
- a) preparing a solution of valsartan in n-butyl acetate;
  - b) crystallizing the crystalline form from the solution; and
  - c) recovering the crystalline form.
- 10 57. The process of claim 56, wherein crystallizing is carried out by cooling to a temperature of about negative 10°C to about 10°C.
58. The process of claim 56, further comprising the step of drying.
59. A crystalline form of Valsartan, wherein the crystalline form (Form XI) is characterized by an XRD pattern with peaks at 5.2, 10.5, 12.9, 13.9,  $18.8 \pm 0.2$  degrees 2 theta.
- 15 60. The crystalline form of claim 59, wherein the crystalline form is further characterized by peaks at 9.7, 16.1, 20.7, 22.9,  $24.1 \pm 0.2$  degrees 2 theta degrees two-theta.
61. The crystalline form of claim 60, wherein the crystalline form is characterized by  
20 the XRD pattern as substantially depicted in Figure 21.
62. A process for preparing crystalline valsartan of claim 59 comprising the steps of contacting a crystalline form of valsartan with toluene to obtain a transformation in the crystalline form.
63. The process of claim 62, wherein the contacting is carried out by trituration.
- 25 64. The process of claim 63, wherein the crystalline form triturated is Form II.
65. The process of claim 62, wherein the trituration is carried out at a temperature of about 40°C to about 60°C, followed by cooling to a temperature of about negative 10°C to about 10°C.
66. The process of claim 62, wherein contacting is carried out by placing crystalline  
30 valsartan in toluene vapor atmosphere.
67. The process of claim 66, wherein the form contacted is Form VII.
68. A process for preparing amorphous valsartan comprising the steps of:
- a) preparing a solution of valsartan in ethyl acetate;

- b) cooling the solution;
  - c) recovering a solid from the ethyl acetate; and
  - d) drying the solid to obtain amorphous valsartan.
69. The process of claim 68, wherein the solution is cooled to a temperature of about  
5 negative 20°C to about 20°C.
70. The process of claim 68, further comprising the step of seeding the solution.
71. The process of claim 68, wherein the drying is carried out at a temperature of about  
10 40°C to about 50°C
72. A process for preparing amorphous valsartan comprising the step of heating  
crystalline valsartan Form I.
73. A process for preparing amorphous valsartan comprising the steps of contacting a  
crystalline form of valsartan with hexane vapor atmosphere to obtain a crystalline  
transformation, and recovering the transformed crystalline form.
74. The process of claim 73, wherein the form contacted is selected from the group  
15 consisting of Form VI and Form VII.
75. A crystalline form of valsartan, wherein the crystalline form is a solvate of heptane.
76. A crystalline form of Valsartan (Form XIII), wherein the crystalline form is  
characterized by an XRD pattern with peaks at 5.1, 11.6, 15.8, 18.6, 26.2 ±0.2  
degrees 2 theta.
77. The crystalline form of claim 76, wherein the crystalline form is further  
characterized by peaks at 10.4, 15.3, 16.4, 19.9, 23.8 ±0.2 degrees two-theta.
78. The crystalline form of claim 77, wherein the crystalline form is characterized by  
the XRD pattern as substantially depicted in Figure 22.
79. A process for preparing crystalline valsartan of claim 76 comprising the steps of  
20 contacting valsartan in solid state with a water vapor atmosphere to obtain a  
transformation to the crystalline form.
80. The process of claim 79, wherein the valsartan contacted is selected from the group  
consisting of III, VI, VII, VIII, IX or amorphous form.
81. A crystalline form of valsartan, wherein the crystalline form is a hydrate.
82. A pharmaceutical composition comprising valsartan in the solid state with a  
thermogram lacking a melting point above about 1 J/g, and a pharmaceutically  
30 acceptable excipient.

83. A method for treating hypertension in a mammal comprising the step of administering the pharmaceutical composition of claim 82 to the mammal in need thereof.
84. A pharmaceutical composition comprising a crystalline valsartan selected from the group consisting of Form II, III, IV, VI, VII, VIII, IX, X, XI and XIII, and a pharmaceutically acceptable excipient.
- 5
85. A method for treating hypertension comprising the step of administering the pharmaceutical composition of claim 84 to the mammal in need thereof.

10

15

20

25

30